REMARKS/ARGUMENTS

Claims 54, 55, 64, 66, 68 and 69 are pending. Claims 1-53, 56-63, 65, 67 and 70 have been cancelled without intending to abandon or to dedicate to the public any patentable subject matter.

Finality of Office Action

The Examiner has made the Office Action mailed January 9, 2008 final. Applicants submit that this is an improper final rejection and request that the Examiner reconsider and withdraw the finality of this Office Action.

In the Office Action, the Examiner has rejected Claims 1-43, which were not amended by Applicants in the last response, and Applicant's therefore submit that amendments did not necessitate the final rejection.

Further, the reference the Examiner is applying (Bruder, U.S. Patent No. 6,391,612) was not previously cited against the claims during the prosecution of this application, and was submitted by Applicants in an Information Disclosure Statement (filed March 19, 2007) prior to the first Office Action on the merits. The Examiner initialed this entry in the Information Disclosure Statement indicating the Examiner's review of this reference prior to issuing the first Office Action on the merits. Therefore, this reference does not represent a reference cited by Applicants during the period after the first Office Action issued.

In light of this prosecution history of the instant application, Applicants submit that the finality of the Office Action mailed January 9, 2008 is untimely and request that the Examiner withdraw the finality of this Office Action.

Claim Rejections Under 35 U.S.C. § 102

The Examiner has rejected Claims 1-43, 65, 67 and 70 under 35 U.S.C. § 102(e) as being anticipated by Bruder (U.S. Patent No. 6,391,612). By this amendment, Applicants have cancelled Claims 1-43, 65, 67 and 70. Applicants therefore submit that the Examiner's rejection of these claims under 35 U.S.C. § 102(e) is moot in light of these cancellations.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected Claims 45-50, 54-55, 64, 66 and 68-70 under 35 U.S.C. § 112, first paragraph, as lacking enablement as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As noted above, Applicants have cancelled Claims 45-50 and 70. Applicants have therefore limited the following remarks to the Examiner's rejections and reasoning as applied only to Claims 54, 55, 64, 66, 68 and 69.

By the amendments made in the Response filed October 18, 2007, and the claim cancellations made in this Amendment, Applicants have limited the claimed subject matter to the use of Fas ligand as the apoptosis-inducing protein, where applicable, and to the use of CrmA as the apoptosis-inhibiting protein, where applicable. In addition, the pending claims have been amended to require the introduction of the viral vector at or adjacent to the site of the cancer cells in the mammal.

The Examiner argues that the specification provides no support for a method of inducing apoptosis in cancer cells of a recipient mammal by introducing into the mammal a recombinant viral vector that encodes Fas ligand.

The first paragraph of § 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained therein." In re Marzocchi, 169 USPQ 367, 369 (C.C.P.A 1971). Further, a specification "may be enabling even though some experimentation is necessary," United States v. Teletronics, Inc., 857 F.2d 778, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), so long as the amount of experimentation required is not "undue experimentation." In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test is whether the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). With this standard in mind, the lack of enablement arguments raised by the Examiner are discussed below.

With respect to the instant application, the specification and working Examples 11-13, Figures 3 and 4 and Tables 2 and 3 provide ample support for the full scope of the claimed method. These examples demonstrate:

1) that a recombinant viral vector encoding Fas ligand can be efficiently transduced into and expressed by mammalian cells, including tumor cells, both *in vitro* and *in vivo*;
2) that both mouse and human Fas ligand expressed by a recombinant viral vector induced apoptosis in a variety of different cells *in vitro*;
3) expression of recombinant Fas ligand in tumor cells *in vivo* inhibited tumor growth and tumor size, including in tumor cells that were resistant to Fas ligand *in vitro*; and
4) injection of recombinant viral vector encoding Fas ligand into existing tumor cells *in vivo* induced apoptosis at the site of the tumor.

Additionally, as discussed in Example 13, the inventors have also discovered that, in addition to the direct anti-tumor effects of Fas ligand on tumors, the effects of Fas ligand appeared to also be due in part to an apoptotic effect on other cells at the site of injection, such as neutrophils, which then potentiated an inflammatory anti-tumor response and reduced tumor growth/size (this "bystander" effect has been subsequently further validated by multiple investigators, *e.g.,* see Hyer et al., *Cancer Gene Ther.* 10:330-339, 2003). It is also known that the introduction of Fas ligand to a cancer has an apoptotic effect on regulatory T cells (Tregs), which otherwise suppress effector T cells and a beneficial cellular immune response (see, *e.g.,* enclosed abstract by Simon et al., *Eur. J. Immunol.* 37:758-767, 2007). Therefore, Fas ligand elimination of Tregs also potentiates the above-mentioned anti-tumor immune response observed by the present inventors and described in the specification. The Examiner should also note that the data in the present specification demonstrate that not all tumor cells in a tumor have to be infected by the Fas ligand-encoding vector to be killed as a result of the administration of the Fas ligand, due to the bystander effect observed by the inventors.

Accordingly, the specification demonstrates that Fas ligand can be effectively introduced into a mammal, into or adjacent a tumor, and efficiently expressed to inhibit tumor growth and tumor size. This supports the full scope of the pending claims, and the Examiner has not provided any evidence or reason to doubt the objective truth of the statements and data contained in the instant application, other than to argue that gene therapy is an inherently unpredictable art. Applicants submit that while the art of gene therapy may have been inherently unpredictable and is becoming more predictable, the current or past state of unpredictability is irrelevant where, as here, the Applicants' examples have demonstrated the efficacy of the claimed subject matter.

Additionally, the Examiner argues that the gene transfer studies provided in Applicants' examples are insufficiently predictive of successful *in vivo* gene therapy. Initially, as described above, Applicants have demonstrated *in vivo* expression of recombinant Fas ligand in tumor cells leading to *in vivo* inhibition of tumor growth and tumor size. Furthermore, Applicants submit that they are not required to show efficacy of the treatment to the degree noted in the Examiner's arguments. As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility. A rigorous or an invariable exact correlation is not required, as stated in Cross v. Iizuka, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). This is true, even when the evidence is in the form of *in vitro* or *in vivo* animal model examples.

Additionally, the Examiner argues that because gene therapy is not considered routine in the art, the experimentation required to practice the claimed invention is extensive and undue. The Examiner also argues that the art of gene therapy is so highly unpredictable that the mere notation of this fact is sufficient to provide a reasonable doubt of the accuracy of the Applicants' statements and data. Presumably this suggests that one of skill in the art provided with the Applicants' *in vitro* and *in vivo* animal model data would still be required to produce a vector containing a nucleic acid sequence encoding CrmA operatively linked to a transcription control sequence and a vector containing a nucleic acid sequence encoding Fas ligand operatively linked to a transcription control sequence and introduce these vectors into a mammal having a tumor, and that this amount of effort is extensive, undue and utterly unpredictable.

But Applicants' data presented in the instant disclosure shows the efficacy of this methodology in the reduction of tumor burden both *in vitro* and *in vivo*. Thus, in this instance, the Examiner is arguing that the reason the highly skilled artisan could not use the well known methods in the art in combination with Applicants' data to extrapolate the working examples provided to human/animal testing and treatment is because it would involve too much work, *i.e.* the work required to make the vectors required in the claimed treatment methods. But this is distinct from too much experimentation. The relevant skill in the art is high, and, as Applicants have described above, the skills required to successfully synthesize a vector are relatively narrow. Thus, there is little experimentation necessary for one of skill in the art to carry out the

known methods necessary to practice the presently claimed invention. Applicants agree with the Examiner that these known methods are labor intensive and require the skilled artisan to perform laboratory work to practice the invention. But this labor, and the work necessary, are not experimentation with an unknown outcome - they are merely the application of known methods by skilled artisans in which the outcome has been shown by working examples in the instant specification. Thus, the Examiner's review of the 'Wands' factors' confuses a labor intensive method with undue experimentation to conclude that the currently claimed methods are not enabled by the present specification. Applicants submit that too much work is not to be equated with undue experimentation and that the working examples and accompanying description provide adequate enablement for the currently claimed methods.

Finally, the Examiner argues that Applicants' previous submission of post-filing publications cannot take the place of evidence lacking in the record and are of no significance regarding what one of skill in the art believed at the filing date of the application. Applicants did not cite the post-filing data to take the place of the evidence that is clearly provided in the instant disclosure. Rather, as clearly stated in Applicants' submission, the post-filing documentation made of record clearly addresses and refutes the Examiner's arguments that the art is so unpredictable as be unbelievable to those of skill in the art presented with Applicants' data and so burdensome as to require undue experimentation. These publications clearly show that the Applicants' experimental work has been replicated and validated both by the Applicants and by independent researchers. This demonstrates that the specification has, in fact, provided a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Additionally, these post-filing references demonstrate that the work required was not undue and it was obviously preformed and shows the efficacy of the treatment in additional animal models, including malignant melanoma in dogs. These references clearly show that the Applicants' experiments have been validated and successfully applied and thus were clearly accepted and followed by those skilled in the art in direct contrast to the Examiner's argument that those of skill in the art could not believe the accuracy or efficacy of Applicants' data in the instant disclosure.

In view of the foregoing remarks, Applicants submit that there is adequate enablement in the specification for Claims 54, 55, 64, 66, 68 and 69 and request the Examiner's rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Based upon the foregoing, Applicants believe that all pending claims are in condition for allowance and such disposition is respectfully requested. In the event that a telephone conversation would further prosecution and/or expedite allowance, the Examiner is invited to contact the undersigned.

Respectfully submitted,

SHERIDAN ROSS P.C.

By: */Robert D. Traver/*
Robert D. Traver
Registration No. 47,999
1560 Broadway, Suite 1200
Denver, Colorado 80202-5141
(303) 863-9700

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